REMARKS

I. STATUS OF THE CLAIMS

Upon entry of this amendment, claims 1, 4, 16-18, 20-26, and 28-30 are pending in this application and are presented for examination. Claims 2-3, 5-15, 19, and 27 have been canceled without prejudice to future prosecution. Claims 1, 4, 16-18, 20, 23-26, and 28 have been amended.

Support for the amendments to claims 1 and 23 is found, for example, on page 30, line 22 to page 32, line 17; on page 49, lines 4-22; and in claim 19 as originally filed. Claims 4, 16-18, and 24-26 have been amended to establish proper antecedent basis for the term "SNP 13 allele" and/or to delete the phrase "independent of small bowel involvement" from the claims. Claim 20 has been amended to establish proper dependency from claim 1. Claim 28 has been amended to establish proper dependency from claim 23.

Accordingly, no new matter has been introduced with the foregoing amendments. Reconsideration is respectfully requested.

II. REJECTION UNDER 35 U.S.C. § 101

Claims 1, 4, and 16-30 were rejected under 35 U.S.C. § 101 as allegedly being directed to non-statutory subject matter. The Examiner alleges that the instant claims are not directed to patent-eligible subject matter because they do not satisfy the *Bilski* "machine-or-transformation test" (*see,* Office Action at page 4). To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

In an earnest effort to expedite prosecution and without acquiescing on the merits of the present rejection, Applicants have amended the claims to recite methods of diagnosing or predicting susceptibility to a clinical subtype of Crohn's disease characterized by fibrostenosing disease, as well as optimizing therapy for an individual having the fibrostenosing clinical subtype, comprising ***genotyping*** an individual for the presence or absence of the SNP 13 allele in the NOD2/CARD15 gene ***using enzymatic amplification*** of nucleic acid from the individual.

Contrary to the Examiner's allegation, this "genotyping" step does indeed meet the *Bilski* test because it is tied to a particular machine or apparatus. In particular, the instant specification discloses that this step may be performed on an ABI 7900 instrument, which uses PCR enzymatic amplification of nucleic acid from an individual to detect the presence or absence of SNPs (*see, e.g.,* Example II at page 49). As a result, this step clearly satisfies the *Bilski* test because genotyping an individual for the presence or absence of the SNP 13 allele requires the use of a particular machine or apparatus such as a thermal cycler or PCR-based instrument for enzymatically amplifying the individual's nucleic acid.

Furthermore, the "genotyping" step set forth in the present claims meets the *Bilski* test because it transforms a particular article into a different state or thing. In particular, this step transforms an individual's nucleic acid into amplified nucleic acid suitable for detecting the presence or absence of the SNP 13 allele. As such, this step clearly satisfies the *Bilski* test because genotyping an individual for the presence or absence of the SNP 13 allele requires the transformation of a particular article (*i.e.,* an individual's nucleic acid) into a different state or thing (*i.e.,* amplified nucleic acid, or multiple copies).

In view of the foregoing, Applicants respectfully request that the Examiner withdraw the present rejection under 35 U.S.C. § 101.

III. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1, 4, and 16-30 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

According to the Examiner, Hirschhorn *et al.* (*Genetics in Medicine*, 4:45-61 (2002)) teaches that only 6 of the 166 putative associations which have been studied three or more times have been consistently replicated and cautions against drawing conclusion from a single report of an association between a genetic variant and disease susceptibility (*see,* Office Action at page 7).

In response, Applicants submit that the teaching of Hirschhorn *et al.* actually supports the reproducibility of Applicants' discovery that the presence of the ***SNP 13 allele*** is

diagnostic of or predictive of susceptibility to the fibrostenosing clinical subtype of Crohn's disease. Example V at page 58 of the instant specification demonstrates that the presence of the ***SNP 13 allele*** had the greatest association with the fibrostenosing clinical subtype of Crohn's disease in a combined cohort ($p = 0.006$). Similarly, Kugathasan *et al.* (*Gastroenterology*, 126, No. 4, Supp. 2, p. A-68, 524) teaches that the ***SNP 13 allele*** ("L1007FsinsC") was strongly associated with early onset and fibrostenosing behavior in pediatric Crohn's disease. Furthermore, Vavassori *et al.* (*Inflamm. Bowel. Dis.*, 10:116-121 (2004)) at page 119, left column, teaches that the ***SNP 13 allele*** ("Leu1007fsinsC") was significantly associated with a fibrostenosing disease of the distal ileum. As such, Applicants' findings are **not** based on conclusions from a single report of an association between a genetic variant and disease susceptibility, but have been **consistently reproduced** in at least three independent studies.

The Examiner further alleges that Ioannidis *et al.* (*Nature Genetics*, 29:306-309 (2001)) teaches that the results of a first study correlate only modestly with subsequent research on the same association (*see,* Office Action at page 8). However, contrary to the teaching of Ioannidis *et al.*, Applicants have discovered that the results of the first study (*i.e.,* Example V of the instant specification) have a substantial degree of correlation with subsequent research on the same association (*e.g.,* Kugathasan *et al.* and Vavassori *et al.*). Thus, Applicants believe that the teaching of Ioannidis *et al.* is inapplicable to the genetic association discovered by Applicants.

With regard to Thisted (May 1998), the Examiner alleges that this reference teaches that only *p*-values less than 0.05 are statistically significant and correspond to real differences between two groups rather than pure chance (*see,* Office Action at page 8). In this regard, Applicants respectfully point out that the *p*-value obtained for the association between the ***SNP 13 allele*** and the fibrostenotic subtype of Crohn's disease in a combined cohort as set forth in Example V of the instant specification ($p = 0.006$) is nearly 10 orders of magnitude less than 0.05. As such, Applicants' discovery that the presence of the ***SNP 13 allele*** is diagnostic of or predictive of susceptibility to the fibrostenosing clinical subtype of Crohn's disease is clearly **not** based on pure chance, but instead corresponds to real differences between individuals with or without the SNP 13 allele.

Finally, Applicants submit that references such as Meyer *et al.* (U.S. Patent Publication No. 20030092019) are simply irrelevant to the instant claims because Applicants are not claiming that all SNPs within the NOD2/CARD15 gene are associated with the fibrostenotic subtype of Crohn's disease. Rather, the instant claims are focused on genotyping an individual for the presence or absence of the ***SNP 13 allele***, and indicating that the presence of this specific allele is diagnostic of or predictive of susceptibility to the fibrostenotic subtype of Crohn's disease.

In view of the foregoing, Applicants assert that the presently claimed methods are sufficiently enabled as of the filing date of the instant application. Importantly, the study set forth in Example V of the instant specification, together with the studies described in Kugathasan *et al.* and Vavassori *et al.* unequivocally establish that the association between the the ***SNP 13 allele*** and the fibrostenosing clinical subtype of Crohn's disease is both predicable and reproducible. Contrary to the Examiner's allegations, other references simply fail to contradict the predictability of the genetic associations recited in the presently claimed methods. As a matter of fact, each of these references actually bolsters the reproducibility of Applicants' discovery. Furthermore, references such as Hirschhorn *et al.* and Ioannidis *et al.* simply fail to challenge the reproducibility of the genetic associations recited in the instant claims.

Accordingly, Applicants respectfully request that the Examiner withdraw the present rejection under 35 U.S.C. § 112, first paragraph.

IV. REJECTIONS UNDER 35 U.S.C. § 102

Claims 1, 4, and 16-20 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Ahmad *et al.* Claims 1, 4, and 16-20 were also rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Radlmayr *et al.* To the extent these rejections apply to the amended claims, Applicants respectfully traverse these rejections.

Applicants respectfully point out that the Examiner's allegation that the 2 references are anticipatory *i.e.*, that Ahmad *et al.* (*Gastroenterology*, 122:854-866 (2002)) at Table 9 on page 862 teaches that the SNP 13 allele ("1007fsinsC") had a highly statistically significant association with the stenotic subtype of Crohn's disease ($p < 0.0001$) and Radlmayr *et*

al. (*Gastroenterology*, 122:2091-2092 (2002)) at Table 1 on page 2092 teaches that the SNP 13 allele ("c-insertion allele") is significantly associated with the fibrostenotic phenotype of Crohn's disease ($p = 0.023$), actually supports Applicants' enablement arguments above. That is, if these references are truly anticipatory, *and Applicants maintain they are not*, their teachings are consistent and support Applicants' findings of an association between the genetic variant as claimed and disease susceptibility. Again, these finding have been **consistently reproduced** in several independent studies.

However, as is clear from Abreu *et al.*, *Gastroenterology*, Volume 123, pages 679-688 (2002) ("the Abreu *et al.* Vol. 123 reference") on page 688 right hand column in the footnotes, the manuscript (preprint) was received by the journal on **February 8, 2002**. The currently claimed subject matter is embodied in the Abreu *et al.* Vol. 123 reference. The date of receipt of the manuscript by the journal clearly antedates Ahmad *et al.* (April 2002) as well as Radlmayr *et al.* (June 2002). The date of receipt of **February 8, 2002** of the manuscript coupled with paragraph 12 of Dr. Taylor's 37 C.F.R. § 1.132 Declaration of record, is clearly sufficient to overcome these §102(a) rejections. MPEP § 2132.01 sets forth that a § 1.131 or 1.132 declaration can overcome a §102(a) reference. Applicants submitted Dr. Taylor's Declaration which overcame the Abreu *et al.* Vol. 123 reference. In view of the February 8, 2002 receipt date of this manuscript, Applicants assert that this receipt date coupled with the Declaration is also sufficient to antedate Ahmad *et al.* (April 2002) as well as Radlmayr *et al.* (June 2002).

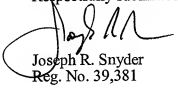
Accordingly, Applicants respectfully request that the Examiner withdraw the present rejections under 35 U.S.C. § 102(a), and send this application to issue.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder
Reg. No. 39,381

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
JCH:jch
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